REMARKS

Applicants wish to thank the Examiner for the courtesy of a telephonic interview on July 25, 2006 regarding the compound 5 species election by the previous counsel. When the previous counsel elected compound 5 in their Office Action response dated January 30, 2006, they identified the subgenus to which the elected compound belongs as subgenus G2 (wherein "[t]he 'molecule comprising B-10' is a peptide or amino acid"), instead of the correct subgenus G3 (wherein "[t]he 'molecule comprising B-10' is a carbohydrate or nucleoside or carborane"). Applicants have prepared the response with the understanding that the species election is compound 5, which is a member of subgenus G3.

Claims 1-71 were pending. The Examiner withdrew claims 1-68 and 70-71 from consideration. The Examiner rejected claim 69 under 35 U.S.C. § 112, first and second paragraphs and under § 103. Applicants have herein amended claim 69; cancelled claims 1-68; amended withdrawn claim 70; and added new claims 75-78, 80, and 82-89. In addition, claims 79, 81, and 90-141 are newly added, but have been withdrawn as they are directed to a non-elected invention. The claims as filed and the specification support the amended and new claims. No new matter has been added. Accordingly, claims 69, 75-78, 80, and 82-89 are pending.

Claims 69, 75-78, 80, and 82-89 read on the elected invention (Group 6, subgenus G3, election of a species comprising (a) compound 5 (found in figures 2 and 3), (b) the pharmaceutically acceptable vehicle water, (c) (i) a method of treating a tumor without imaging the tumor, and (d) the anatomical location of the tumor is the lung). In light of the amendments and the remarks herein, Applicants respectfully request reconsideration and allowance of claims 69, 75-78, 80, and 82-89.

The Examiner has required an election of species between treatment and imaging claims as well as an election of a particular compound. Applicants have herein withdrawn claims 70-71, 79, 81, and 90-141 as drawn to a non-elected invention, but have concurrently amended the independent withdrawn claims to incorporate all the limitations of the pending claims.

Applicants respectfully request rejoinder of all withdrawn imaging claims (i.e., claims 70-71 and 109-141) upon allowability of an examined treatment claim.

Amendment for Figure 1

As shown in *The Merck Index*, Merck and Co. (11th Ed., 1989), a copy of which is attached, a methyl group appears on carbon 1 of ring A. Figure 1 was adapted from *The Merck Index*, as detailed in the specification on page 2. In the original Figure 1, however, a hydrogen appears on carbon 1 of ring A instead of the methyl group depicted in *The Merck Index*. Since the cobalamin structure was well known at the time the application was filed, the depiction of that structure in original Figure 1 would have been recognized by those of ordinary skill in the art as a mere inadvertent clerical error. The proposed amendment to Figure 1 is further supported by the attached references: (1) *B_{12} **vol. 1***, D. Dolphin, Ed. (1982, pp. 17-21), a reference referred to by the above-referenced *The Merck Index*; and (2) Bernhauer, K., Müller, O., and Wagner, F., *Angew. Chem. Int. Ed.* **1964**, 3(3), 200. The proposed amendment to Figure 1 does not constitute new matter. Applicants respectfully request acceptance of the amended Figure 1.

Request for Review of Supplemental Information Disclosure Statement

Applicants herein provide a Supplemental Information Disclosure Statement to address the Examiner's objection to certain references provided in a prior PTO Form 1449. Applicants respectfully request consideration of the attached Supplemental Information Disclosure Statement and initialing of the PTO Form 1449.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claim 69 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Specifically, the Examiner raised two questions: "(a) will the compounds of claim 1

sequester in cancerous tissue when the cobalamin moiety is intact? and (b) will the compounds of claim 1 sequester in cancerous tissue if only a "residue" of the cobalamin is used?" The Examiner further stated that "there is no reason to believe that any selective binding of the compounds to cancerous tissue will occur when the cobalamin moiety is intact, and certainly, there is no reason to believe that a small substituent such as acetamide or ethanol or phosphate will bind selectively to cancerous tissue. In the absence of selective binding, the skilled oncologist would not believe that an effective anti-tumor therapy can be achieved."

Applicants respectfully traverse the rejection. The factors required to support an enablement rejection and to determine whether any necessary experimentation is "undue" include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed Cir. 1988). Furthermore, a conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993).

Applicants note that the background of the specification cites relevant references which fully detail the ability of cobalamin to be taken-up by cancerous cells; for example, see page 3 paragraph 29, which states:

> Cells undergoing rapid proliferation have been shown to have increased uptake of thymidine and methionine (See, for example, M.E. van Eijkeren et al., *Acta Oncologica*, 31, 539 (1992); K. Kobota et al., *J. Nucl. Med.*, 32, 2118 (1991) and K. Higashi et al., *J. Nucl. Med.*, 34, 773 (1993)). Since methylcobalamin is directly involved with methionine synthesis and indirectly involved in the synthesis of thymidylate and DNA, it is not

surprising that methylcobalamin as well as Cobalt-57-cyanocobalamin have also been shown to have increased uptake in rapidly dividing tissue (for example, see, B.A. Cooper et al., *Nature*, 191, 393 (1961); H. Flodh, *Acta Radiol. Suppl.*, 284, 55 (1968); L. Bloomquist et al., *Experientia*, 25, 294 (1969)).

Applicants also refer to Example 4 which details the results of an *in vitro* biological activity assay in which the compounds of the current disclosure, specifically carborane cyanocobalamin analogs, were shown to be capable of competitively blocking Co-57-cyanocobalamin from binding to transcobalamin proteins. The ability of these analogs to successfully block binding of the Co-57-cyanocobalamin to transcobalamin proteins resulted in an average percent binding to transcobalamin protein for the carborane-d cyanocobalamin and carborane-b cyanocobalamin of 37.75% and 92.93% respectively. This binding result clearly has significant application in cells undergoing rapid proliferation where cobalamin uptake is increased.

Moreover, the efficiency of tumor uptake of other cobalamin derivatives, specifically cobalamin linked to chelating groups, has been demonstrated in Collins, D.A., *et al.* U.S. Patent Number 5,739,313, Example 9. This Example demonstrated that absorption of the cobalamin derivative in tumors was *10-20 times greater* than that of the chelating group alone. Given all of the above, Applicants respectfully assert that the specification has enabled the full scope of the claims at issue, providing both guidance and considerable direction, given the level of the skill in the art and the state of the prior art at the time of filing of the application. See In re Wands, 858 F.2d at 740, 8 U.S.P.Q.2d at 1406. Therefore, one of ordinary skill in the art would reasonably understand the claimed methods, which include administration of cobalamin derivatives, to function as described, with localization of the administered compounds occurring at the site of a tumor. In response to the second part of the rejection in which the Examiner construed the term "residue" in the claim to include "acetamide or ethanol or phosphate," Applicants have deleted the term "residue" throughout the claims. Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claim 69 as being indefinite under 35 U.S.C § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. The Examiner detailed four distinct issues which prompted the rejection; each of them will be discussed in turn.

First, the Examiner stated that claim 69 was dependent on a non-elected claim. Applicants have amended the claim to remove such a dependence.

Second, the Examiner stated that the formula (of Figure 1) should be provided in claim 69. Applicants have amended the claim to include the structure of formula I.

Third, the Examiner rejected claim 69 as being "indefinite as to the process steps of 'administering neutron capture therapy'." Specifically, the Examiner asked "[w]hat does the medical practitioner do, and what does he (or she) see? Does the neutron capture therapy require any external energy source? Does the neutron capture therapy require administration of a compound, either claimed or not claimed?"

The test for definiteness is:

> [W]hether one skilled in the art would understand the bounds of the claim when read in light of the specification. . . . If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more. . . . The degree of precision necessary for adequate claims is a function of the nature of the subject matter.

Miles Laboratories, Inc. v. Shandon Inc., 997 F.2d 870, 27 U.S.P.Q.2d 1123 (Fed. Cir. 1993), *cert. denied*, 510 U.S. 1100 (1994). Applicants note that the present specification itself notes that boron neutron capture therapy has been in use as a therapeutic method for over 50 years. The general details of boron neutron capture therapy (see, e.g., Page 1, paragraph 3) are described as:

> [A] two component or binary system, consisting of ^{10}B and thermal neutrons, which when combined together generate high linear energy

> transfer (LET) radiation capable of selectively destroying tumor cells without significant damage to normal tissues. In order for BNCT [boron neutron capture therapy] to succeed a critical amount of ^{10}B and a sufficient number of thermal neutrons must be delivered to individual tumor cells.

Collins et al. (U.S. Publication No. 2004/0162240) page 1, paragraph 6.

In addition, Spielvogel *et al.*(U.S. Patent No. 5,130,302) also demonstrates the state of the art of boron neutron capture therapy at column 1, lines 46-65. Speilvogel generally describes boron neutron capture therapy as follows:

> Boron containing compounds are also useful in an antineoplastic regimen known as Boron Neutron Capture Therapy (BNCT). Soloway, A.H., *Progress in Boron chemistry*; Steinberg, H., McCloskey, A.L., Eds.; the Macmillam Company: New York, 1964; Vol. 1, Chapter 4, 203-234. BNCT requires two components (Boron-10 and low energy thermal neutrons) for a radiotoxic reaction. The inherent advantage is that each component can be manipulated independently to produce the desired radiation effect. Boron-10 has a high cross section for thermal neutrons and after neutron capture, the particles generated, Li & α, are relatively large by radiation standards and thus have a relatively short attack on tissue, 10-14 microns. The Boron-10 is non-radioactive and for use in BNCT, its compounds do not have to be cytotoxic towards tumor cells. Thermal neutrons have such low energy that they cannot ionize tissue components per se. Upon neutron capture, however, the energy generated is sufficient to destroy the cell.

Spielvogel *et al.* (U.S. Patent No. 5,130,302) col. 1, lines 46-65.

Therefore, Applicants respectfully assert that the process steps of neutron capture therapy were well understood by those of ordinary skill in the art, and the methods of treatment could be readily practiced in view of the present disclosure and the knowledge generally available in the art.

Finally, the Examiner rejected claim 69 as being indefinite due to its dependence on claim 1. Applicants have cancelled claim 1 and removed the dependence of claim 69 on claim 1.

In light of the above arguments, the Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 103

The Examiner rejected claim 69 under 35 U.S.C. § 103 as being unpatentable over Glass *et al.*, U.S. Patent No. 6,107,902 ("Glass"); Griffen *et al.*, U.S. Patent No. 5,630,786 ("Griffen"); or Schinazi *et al.*, U.S. Patent No. 5,599,796 ("Schinazi"). The Examiner stated that "[t]he issue here is that which is meant by the term 'residue' in instant claim 1." Applicants have deleted the term "residue" in reference to either the compound of formula I or in reference to a B-10 containing compound. Claim 69, as amended, reads "[a] method of treating a tumor in a mammal comprising: (a) administering to the mammal an effective amount of a compound of formula I linked to a molecule comprising B-10 wherein X is CN, OH, CH_3, adenosyl, or a molecule comprising B-10; or a pharmaceutically acceptable vehicle; and (b) administering neutron capture therapy." Since Glass, Griffen, and Schinazi, whether considered alone or even in combination, fail to teach or suggest each and every element of claim 69, Applicants respectfully request withdrawal of these rejections.

The Examiner also rejected claim 69 under 35 U.S.C. § 103 as being unpatentable over Collins (U.S. Patent No. 6,004,533) ("Collins") in view of Schinazi. In particular, the Examiner stated: "Collins discloses compounds in which cyanocobalamin is linked to a diagnostic radionuclide. Collins does not disclose compounds in which cyanocobalamin is linked to boron-10." The Examiner went on to state, however, that it would have been "obvious to one of

ordinary skill to link B10 to cyanocobalamin to achieve the therapeutic benefits asserted by Schinazi."

Applicants respectfully disagree, however, as the combination of the cited references fail to teach or suggest the presently claimed methods. Proper analysis under § 103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition, and (2) whether the prior art would also have revealed that in so making, those of ordinary skill would have had a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). According to the M.P.E.P. § 2143.01(V-VI), there is no motivation to combine references where (a) the proposed combination would render the device or method inoperative for its intended purpose or (b) one of the references teaches away from the combination. Neither of the cited references, either alone or in combination, teach or suggest the presently claimed method.

As indicated above, claim 69 recites: "[a] method of treating a tumor in a mammal comprising: (a) administering to the mammal an effective amount of a compound of formula I linked to a molecule comprising B-10 wherein X is CN, OH, CH_3, adenosyl, or a molecule comprising B-10; or a pharmaceutically acceptable vehicle; and (b) administering neutron capture therapy."

Collins discloses, in part, processes for imaging tumors and organs comprising administering compounds in which cobalamin is linked to a group containing a detectable radionuclide. B-10, however, is stable and not detectable by normal decay. Consequently, one of ordinary skill in the art would not expect a cobalamin derivative of Collins in which the radionuclide was replaced with B-10 to be detectable or useful for imaging. Since this modification would make the Collins compounds unsuitable for their intended purpose, one of ordinary skill in the art would not be motivated to combine Collins and Schinazi as asserted. Therefore, the instant rejection is improper and should be withdrawn.

Furthermore, even if one were to so modify the cobalamin moiety of Collins, one of ordinary skill in the art would not have had a reasonable expectation of successfully achieving therapeutic benefits. Cobalamin is generally considered to be hydrophilic (see, e.g., *The Merck*

Index (11th Ed., 1989), which cites the solubility of cobalamin as 1 g in 80 mL of water). In addition, cobalamin uptake into cancer cells may require binding to a serum protein. By contrast, Schinazi teaches that suitable compounds must be lipophilic (see, e.g., col. 5, lines 54-56, "[t]he prostate glad is *impermeable* to many compounds *unless* they are *lipophilic* and delivered unbound to serum proteins.") According to Schinazi, a compound must be "sufficiently lipophilic to pass through the appropriate urogenital membranes in a quantity high enough to achieve therapy on irradiation with low-energy neutrons" (col. 6, lines 14-19). Given the teachings of Schinazi, a person having ordinary skill in the art would have expected the carborane moiety of Schinazi to dramatically affect the hydrophobicity of cobalamin and its ability to be bound to serum transport proteins. Similarly, modifying the compounds of Schinazi to include a hydrophilic cobalamin would render Schinazi compounds unable to cross "appropriate urogenital membranes." Thus, after reviewing Collins and Schinazi, one of ordinary skill in the art would not have expected cobalamin compounds linked to B-10 to be taken up by prostate cancer cells in sufficient quantities to be therapeutic.

Accordingly, Applicants respectfully assert that the claims are not obvious, and request withdrawal of the rejections under 35 U.S.C. § 103.

CONCLUSION

Given all of the above, Applicants respectfully request reconsideration and allowance of the pending claims. The Examiner is invited to call the under-signed attorney if such would expedite prosecution.

Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

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Amendments to the Drawings:

The attached replacement sheet of drawings includes an amended Figure 1 and replaces the original sheet including Figure 1.

Attachments following last page of this Amendment:

Replacement Sheet (1 pages)
Annotated Sheet Showing Change (1 pages)

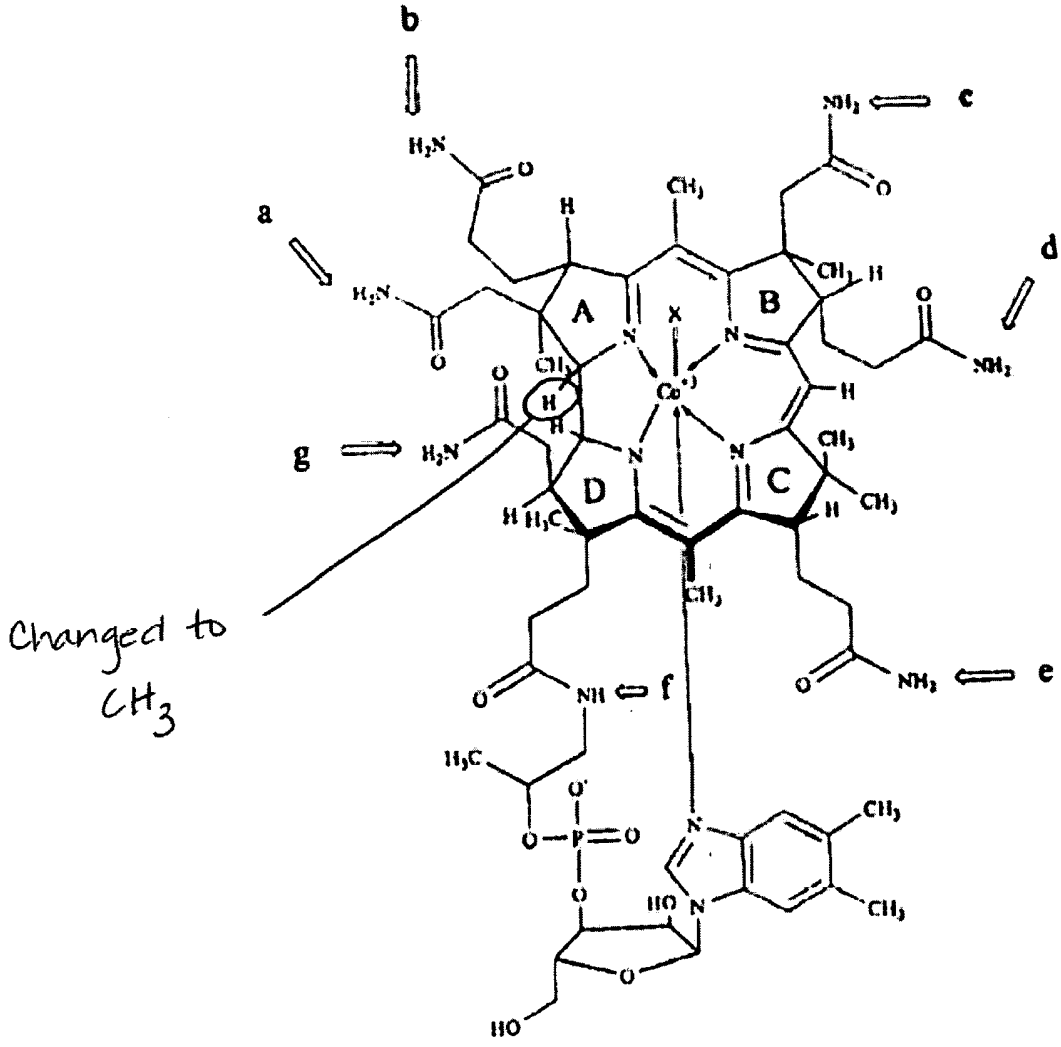

FIGURE 1